Naval Medical Center Portsmouth (NMCP) COVID-19 Literature Report #94: Thursday, 26 May 2022

This report is a day early because of the Memorial holiday. Have a safe one!

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Purpose: These reports, published every other week on Fridays, are curated collections of current research, special reports, and news regarding the COVID-19 pandemic that may be of interest to medical providers, leadership, and decision makers.

All reports are available online at https://nmcp.libguides.com/covidreport. Access is private; you will need to use the direct link or bookmark the URL.

Disclaimer: I am not a medical professional. This document is current as of the date noted above. While I make every effort to find and summarize available data, I cannot cover everything in the literature on COVID-19. Due to the rapid evolution of the literature, I will not update past reports when new information arises; for retracted papers specific to COVID-19, see the list of retracted papers from Retraction Watch.

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A Brief Note and Request

The NMCP COVID-19 Literature Report has been produced for over 2 years. What started out as temporary and short document to share information on an emerging disease has evolved to a long form collection of COVID-related items from a variety of sources.

These reports take significant time and effort to produce. As the 100th issue approaches, I want to touch base with the people who read the reports and ask:

- What value do these report have to you? Have they made a difference in decision making or impacted patient care?
- Should these reports continue?
- If they do, how can they best support what you need?

I welcome your opinions, suggestions, or any other constructive feedback regarding these reports (email usn.hampton-roads.navhospporsva.list.nmcp-library@mail.mil). Thank you!

The Big Picture

News in Brief

"Nation's latest COVID-19 wave largely hidden from view, health experts say: 'There's a lot of COVID out there,' one expert acknowledged" (ABC).

Preparedness

"Want to prevent pandemics? Stop spillovers: Decision-makers discussing landmark agreements on health and biodiversity must include four actions to reduce the risk of animals and people exchanging viruses" (Nature).

Funding

"States have yet to spend hundreds of millions of federal dollars to tackle Covid health disparities" (KHN).

"'A lot of unnecessary loss of life': The White House's dire warning on Covid-19 funding" (Vox).

Long Reads

"The pandemic's true health cost: how much of our lives has COVID stolen?" (Nature)

Journal Articles

J Trauma Acute Care Surg: The National Disaster Medical System and Military Combat Readiness - A Scoping Review (23 May 2022)

> "A scoping review was conducted to describe the history of the National Disaster Medical System (NDMS) in the context of U.S. military medical preparedness for a large-scale overseas military conflict. NDMS civilian hospitals would serve as backups to military treatment facilities if both U.S. Department of Defense and U.S. Department of Veterans Affairs hospitals reached capacity during such a conflict.
>
> Systematic searches were used to identify published works discussing the NDMS in the scientific and grey literature. Results were limited to publicly available unclassified English language works from 1978 to January 2022; no other restrictions were placed on the types of published works. Full-text reviews were conducted on identified works (except student papers and dissertations) to determine the extent to which they addressed NDMS definitive care. Data charting was performed on a final set of papers to assess how these works addressed NDMS definitive care.
>
> The search identified 54 works published between 1984 and 2022. More than half of the publications were simple descriptions of the NDMS (54%, n = 29), and most were published in academic or professional journals (70%, n = 38). Only nine constituted original research. There were recurrent criticisms of and recommendations for improving the definitive care component of the NDMS. The lack of published literature on NDMS definitive care supports the assertion that the present-day NDMS may lack the capacity and military-civilian interoperability necessary to manage the casualties resulting from a large-scale overseas military conflict."

JAMA Netw Open: Association Between the COVID-19 Pandemic and Disparities in Access to Major Surgery in the US (23 May 2022)

> "Question: What is the association between the Centers for Medicare & Medicaid Services moratorium on elective operations during the first wave of the COVID-19 pandemic and changes in the monthly elective surgical case volumes among Black individuals, Asian individuals, and individuals of other races compared with White individuals?
>
> Findings: In this cross-sectional study of 3 470 905 adults undergoing major surgery, the reduction in elective surgery case volumes during the Centers for Medicare & Medicaid Services moratorium was not greater for Black individuals, Asian individuals, and individuals of other races than for White individuals.
>
> Meaning: These findings suggest that the early response to the pandemic did not increase disparities in access to surgical care."

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JAMA Netw Open: Evaluation of Age Patterns of COVID-19 Mortality by Race and Ethnicity From March 2020 to October 2021 in the US (17 May 2022)

> "This cross-sectional study examines age-specific COVID-19 mortality rates in the US from March 2020 to October 2021 by sex and race and ethnicity….
>
> Reductions in COVID-19 mortality among older populations are remarkable. From the second period through the third period, declines in death rates for the various racial and ethnic and sex combinations were especially large among those aged 80 to 84 years and those 85 years or older. Despite the availability of effective vaccines, COVID-19 mortality rose among younger adults."

Mil Med: Analysis of the Virus SARS-CoV-2 as a Potential Bioweapon in Light of International Literature (16 May 2022)

> "Introduction: As of early 2022, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic still represents a worldwide medical emergency situation. The ongoing vaccination programs can slow down the spread of the virus; however, from time to time, the newly emerging variants of concern and antivaccination movements carry the possibility for the disease to remain in our daily lives. After the appearance of SARS-CoV-2, there was scholarly debate whether the virus was of natural origin, or it emerged from a laboratory, some even thinking the agent's potential biological weapon properties suggest the latter scenario. Later, the bioweapon theory was dismissed by the majority of experts, but the question remains that despite its natural origin, how potent a biological weapon the SARS-CoV-2 virus can become over time.
>
> Materials and methods: Based on 12 bioweapon threat assessment criteria already published in 2018, we performed a literature search and review, focusing on relevant potential bioweapon properties of the virus SARS-CoV-2. Instead of utilizing a survey among experts, we tried to qualify and quantify characteristics according to the available data found in peer-reviewed papers. We also identified other key elements not mentioned in the original 12 bioweapon criteria, which can play an important role in assessing future biological weapons.
>
> Results: According to the international literature we analyzed, SARS-CoV-2 is a moderately infectious agent (ID50 estimated between 100 and 1,000), with high infection-to-disease ratio (35%-45% rate of asymptomatic infected) and medium incubation period (1-34 days, mean 6-7 days). Its morbidity and mortality rate can be categorized as medium (high morbidity rate with significant mortality rate). It can be easily produced in large quantities, has high aerosol stability, and has moderate environmental stability. Based on laboratory experiments and statistical model analysis, it can form and is contagious with droplet nuclei, and with spray technique utilization, it could be weaponized effectively. Several prophylactic countermeasures are available in the form of vaccines; however, specific

> therapeutic options are much more limited. In connection with the original assessment criteria, the SARS-CoV-2 only achieved a "0" score on the ease of detection because of readily available, relatively sensitive, and specific rapid antigen tests. Based on the pandemic experience, we also propose three new assessment categories: one that establishes a mean to measure the necessary quarantine restrictions related to a biological agent, another one that can represent the personal protective equipment required to work safely with a particular agent, and a third one that quantifies the overall disruptive capability, based on previous real-life experiences. These factors could further specify the threat level related to potential biological weapons.
>
> Conclusions: Our results show that the virus can become a potent bioweapon candidate in the future, achieving a total score of 24 out of 36 on the original 12 criteria. The SARS-CoV-2 has already proven its pandemic generating potential and, despite worldwide efforts, still remains an imminent threat. In order to be prepared for the future possibility of the virus arising as a bioweapon, we must remain cautious and take the necessary countermeasures."

SARS-CoV-2 Virus and Variants

News in Brief

"ECDC ups BA.4, BA.5 to variants of concern, warns of case rises" (CIDRAP).

"When will we know if COVID is seasonal?" (Medpage)

Journal Articles

NEJM: Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2 (25 May 2022)

> "Background: Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) provides natural immunity against reinfection. Recent studies have shown waning of the immunity provided by the BNT162b2 vaccine. The time course of natural and hybrid immunity is unknown.
>
> Methods: Using the Israeli Ministry of Health database, we extracted data for August and September 2021, when the B.1.617.2 (delta) variant was predominant, on all persons who had been previously infected with SARS-CoV-2 or who had received coronavirus 2019 vaccine. We used Poisson regression with adjustment for confounding factors to compare the rates of infection as a function of time since the last immunity-conferring event.

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> Results: The number of cases of SARS-CoV-2 infection per 100,000 person-days at risk (adjusted rate) increased with the time that had elapsed since vaccination with BNT162b2 or since previous infection. Among unvaccinated persons who had recovered from infection, this rate increased from 10.5 among those who had been infected 4 to less than 6 months previously to 30.2 among those who had been infected 1 year or more previously. Among persons who had received a single dose of vaccine after previous infection, the adjusted rate was low (3.7) among those who had been vaccinated less than 2 months previously but increased to 11.6 among those who had been vaccinated at least 6 months previously. Among previously uninfected persons who had received two doses of vaccine, the adjusted rate increased from 21.1 among those who had been vaccinated less than 2 months previously to 88.9 among those who had been vaccinated at least 6 months previously.
>
> Conclusions: Among persons who had been previously infected with SARS-CoV-2 (regardless of whether they had received any dose of vaccine or whether they had received one dose before or after infection), protection against reinfection decreased as the time increased since the last immunity-conferring event; however, this protection was higher than that conferred after the same time had elapsed since receipt of a second dose of vaccine among previously uninfected persons. A single dose of vaccine after infection reinforced protection against reinfection."

Clin Infect Dis: Understanding 'hybrid immunity': comparison and predictors of humoral immune responses to SARS-CoV-2 infection and COVID-19 vaccines (24 May 2022)

> "Background: Comparing humoral responses in SARS-CoV-2 vaccinees, those with SARS-CoV-2 infection, or combinations of vaccine/infection ('hybrid immunity'), may clarify predictors of vaccine immunogenicity.
>
> Methods: We studied 2660 U.S. Military Health System beneficiaries with a history of SARS-CoV-2 infection-alone (n = 705), vaccination-alone (n = 932), vaccine-after-infection (n = 869), and vaccine-breakthrough-infection (n = 154). Peak anti-spike-IgG responses through 183 days were compared, with adjustment for vaccine product, demography, and comorbidities. We excluded those with evidence of clinical or sub-clinical SARS-CoV-2 reinfection from all groups.
>
> Results: Multivariable regression results indicated vaccine-after-infection anti-spike-IgG responses were higher than infection-alone ($p < 0.01$), regardless of prior infection severity. An increased time between infection and vaccination was associated with a greater post-vaccination IgG response ($p < 0.01$). Vaccination-alone elicited a greater IgG response, but more rapid waning of IgG ($p < 0.01$), compared to infection-alone ($p < 0.01$). BNT162b2 and mRNA-1273 vaccine-receipt was associated with greater IgG responses compared to JNJ-78436735 ($p < 0.01$), regardless of infection history. Those with vaccine-after-infection or

> vaccine-breakthrough-infection had a more durable anti-spike-IgG response compared to infection-alone ($p < 0.01$).
>
> Conclusions: Vaccine-receipt elicited higher anti-spike-IgG responses than infection-alone, although IgG levels waned faster in those vaccinated (compared to infection-alone). Vaccine-after-infection elicits a greater humoral response compared to vaccine or infection alone; and the timing, but not disease severity, of prior infection predicted these post-vaccination IgG responses. While differences between groups were small in magnitude, these results offer insights into vaccine immunogenicity variations that may help inform vaccination timing strategies."

Nature: Limited cross-variant immunity from SARS-CoV-2 Omicron without vaccination (18 May 2022)

> "SARS-CoV-2 Delta and Omicron are globally relevant variants of concern (VOCs). While individuals infected with Delta are at risk to develop severe lung disease, infection with Omicron often causes milder symptoms, especially in vaccinated individuals1,2. The question arises whether widespread Omicron infections could lead to future cross-variant protection, accelerating the end of the pandemic. Here we show that without vaccination, infection with Omicron induces a limited humoral immune response in mice and humans. Sera from mice overexpressing the human ACE2 receptor and infected with Omicron neutralize only Omicron, but no other VOCs, whereas broader cross-variant neutralization was observed after WA1 and Delta infections. Unlike WA1 and Delta, Omicron replicates to low levels in the lungs and brains of infected animals, leading to mild disease with reduced pro-inflammatory cytokine expression and diminished activation of lung-resident T cells. Sera from unvaccinated, Omicron-infected individuals show the same limited neutralization of only Omicron itself. In contrast, Omicron breakthrough infections induce overall higher neutralization titers against all VOCs. Our results demonstrate that Omicron infection enhances preexisting immunity elicited by vaccines but, on its own, may not confer broad protection against non-Omicron variants in unvaccinated individuals."

Emerg Infect Dis: SARS-CoV-2 Delta–Omicron Recombinant Viruses, United States (12 May 2022)

> "To detect new and changing SARS-CoV-2 variants, we investigated candidate Delta–Omicron recombinant genomes from Centers for Disease Control and Prevention national genomic surveillance. Laboratory and bioinformatic investigations identified and validated 9 genetically related SARS-CoV-2 viruses with a hybrid Delta–Omicron spike protein."

Transmission, Exposure, and Surveillance

News in Brief

"The federal government is offering another round of free COVID tests" (NPR; see https://www.covid.gov/tests to order).

"Trained scent dogs detect airline travelers with COVID-19" (CIDRAP; see also: BMJ Global Health article).

Long Reads

""The COVID testing company that missed 96% of cases: State and local officials across Nevada signed agreements with Northshore Clinical Labs, a COVID testing laboratory run by men with local political connections. There was only one problem: Its tests didn't work" (ProPublica).

Journal Articles

Clin Infect Dis: Relative Virulence of SARS-CoV-2 Among Vaccinated and Unvaccinated Individuals Hospitalized with SARS-CoV-2 (25 May 2022)

> "Background: The rapid development of safe and effective vaccines against the SARS-CoV-2 virus has been a singular scientific achievement. Confounding due to health seeking behaviours, circulating variants, and differential testing by vaccination status may bias analyses towards an apparent increase in infection severity following vaccination.
>
> Methods: We used data from Ontario, Canada's Case and Contact Management database, merged to a provincial vaccination dataset (COVaxON) to create a time-matched cohort of individuals who were hospitalized with SARS-CoV-2 infection. Vaccinated individuals were matched to up to five unvaccinated individuals based on test date. Risk of ICU admission and death were evaluated using conditional logistic regression. Unmatched exploratory analyses were performed to identify sources of heterogeneity in vaccine effects.
>
> Results: In 20,064 individuals (3,353 vaccinated and 16,711 unvaccinated) hospitalized with infection due to SARS-CoV-2 between January 1st, 2021 and January 5th, 2022, vaccination with 1, 2, or 3 doses significantly reduced the risk of ICU admission and death. An inverse dose-response relationship was observed between vaccine doses received and both outcomes (adjusted odds ratio (aOR) per additional dose for ICU admission: 0.66, 95% CI 0.62 to 0.71; aOR for death: 0.78, 95% CI 0.72 to 0.84). Reduction in risk was greater for ICU admission than for death (P for heterogeneity <0.05).
>
> Interpretation: We identified decreased virulence of SARS-CoV-2 infections in vaccinated individuals, even when vaccines failed to prevent infection sufficiently severe to cause

> hospitalization. Even with diminished efficacy of vaccines against infection with novel VOCs, vaccines remain an important tool for reduction of ICU admission and mortality."

Clin Infect Dis: Duration of replication-competent SARS-CoV-2 shedding among patients with severe or critical coronavirus disease 2019 (COVID-19) (24 May 2022)

> "Background: Patterns of shedding replication-competent SARS-CoV-2 in severe or critical COVID-19 are not well-characterized. We investigated the duration of replication-competent SARS-CoV-2 shedding in upper and lower airway specimens from patients with severe or critical COVID-19.
>
> Methods: We enrolled patients with active or recent severe or critical COVID-19 who were admitted to a tertiary care hospital intensive care unit (ICU) or long-term acute care hospital (LTACH) because of COVID-19. Respiratory specimens were collected at predefined intervals and tested for SARS-CoV-2 using virus culture and RT-qPCR. Clinical and epidemiologic metadata were reviewed.
>
> Results: We collected 529 respiratory specimens from 78 patients. Replication-competent virus was detected in 4 of 11 (36.3%) immunocompromised patients up to 45 days after symptom onset, and in 1 of 67 (14.9%) immunocompetent patients 10 days after symptom onset (P = 0.001). All culture-positive patients were in the ICU cohort and had persistent or recurrent symptoms of COVID-19. Median time from symptom onset to first specimen collection was 15 days (range, 6-45) for ICU patients and 58.5 days (range, 34-139) for LTACH patients. SARS-CoV-2 RNA was detected in 40 of 50 (80%) ICU patients and 7 of 28 (25%) LTACH patients.
>
> Conclusions: Immunocompromise and persistent or recurrent symptoms were associated with shedding of replication-competent SARS-CoV-2, supporting the need for improving respiratory symptoms in addition to time as criteria for discontinuation of transmission-based precautions. Our results suggest that the period of potential infectiousness among immunocompetent patients with severe or critical COVID-19 may be similar to that reported for patients with milder disease."

JAMA Netw Open: Transmission and Infectious SARS-CoV-2 Shedding Kinetics in Vaccinated and Unvaccinated Individuals (24 May 2022)

> "Question: Do individuals fully vaccinated against COVID-19 have a shorter duration of viable SARS-CoV-2 viral shedding and a lower rate of secondary transmission than in partially vaccinated or unvaccinated individuals?
>
> Findings: In this cohort study of 173 health care workers, inpatients, and guardians and 45 participants in a community facility, secondary transmission of SARS-CoV-2 was significantly less common, and viable virus was detected for a shorter duration in fully vaccinated individuals than in partially vaccinated or unvaccinated individuals.

> Meaning: Fully vaccinated individuals had a shorter duration of viable viral shedding and a lower rate of secondary transmission than partially vaccinated or unvaccinated individuals."

PNAS: Aerosol particle emission increases exponentially above moderate exercise intensity resulting in superemission during maximal exercise (23 May 2022)

> "Many airborne pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are transmitted indoors via aerosol particles. During exercise, pulmonary ventilation can increase over 10-fold, and therefore, exercisers will exhale a greater volume of aerosol-containing air. However, we currently do not know how exercise affects the concentration of aerosol particles in exhaled air and the overall emission of aerosol particles. Consequently, we developed a method to measure in parallel the concentration of aerosol particles in expired air, pulmonary ventilation, and aerosol particle emission at rest and during a graded exercise test to exhaustion. We used this method to test eight women and eight men in a descriptive study. We found that the aerosol particle concentration in expired air increased significantly from 56 ± 53 particles/liter at rest to 633 ± 422 particles/liter at maximal intensity. Aerosol particle emission per subject increased significantly by a factor of 132 from 580 ± 489 particles/min at rest to a super emission of 76,200 ± 48,000 particles/min during maximal exercise. There were no sex differences in aerosol particle emission, but endurance-training subjects emitted significantly more aerosol particles during maximal exercise than untrained subjects. Overall, aerosol particle emission increased moderately up to an exercise intensity of ∼2 W/kg and exponentially thereafter. Together, these data might partly explain superspreader events especially during high-intensity group exercise indoors and suggest that strong infection prevention measures are needed especially during exercise at an intensity that exceeds ∼2 W/kg. Investigations of influencing factors like airway and whole-body hydration status during exercise on aerosol particle generation are needed."

Am J Infect Control: Viral transmissibility of SARS-CoV-2 accelerates in the winter, similarly to influenza epidemics (20 May 2022)

> "Background: The transmissibility of SARS-CoV-2 is anticipated to increase in the winter because of increased viral survival in cold damp air and thus would exacerbate viral spread in community. Analysis to capture the seasonal trend is needed for monitoring, prevention, and controls.
>
> Methods: We compared regression models for the 5-week case prior to each epidemic peak week for both the Covid-19 and influenza epidemics in winter and summer. The weekly case increase ratio was compared, using non-paired t-tests between seasons. In order to test the robustness of seasonal transmission patterns, the normalized weekly case numbers of Covid-19 and influenza case rates of all seasons were assessed in a combined quadratic regression analysis.

> Results: In winter, the weekly case increase ratio accelerated before epidemic peaks, similarly, for both Covid-19 and influenza. The quadratic regression models of weekly cases were observed to be convex curves in the winter and concave curves in the spring/summer for both Covid-19 and influenza. A significant increase of case increase ratio (2.58 [95%CI:0.01-6.37, p=0.049]) of the Covid-19 and influenza epidemics was observed in winter as compared to spring/summer before the epidemic peak.
>
> Conclusions: The epidemic of Covid-19 was found to mirror that of influenza, suggesting a strong underlying seasonal transmissibility. Influenza epidemics can potentially be a useful reference for the Covid-19 epidemics."

COVID-19 Vaccines

News in Brief

"Flu vaccine could cut COVID risk" (Nature; see also: medRxiv preprint).

Journal Articles

Ann Allergy Asthma Immunol: Outcomes of Allergic Type Reactions Following mRNA COVID-19 Vaccination at Three Military Medical Centers (19 May 2022)

> "This is a multicenter retrospective review of patients referred to the Allergy Clinics of the Walter Reed National Military Medical Center, Naval Medical Center Portsmouth, and Womack Army Medical Center, from January 2021 to November 2021 for AEFI [adverse events following immunization] following receipt of either mRNA COVID-19 vaccine…. There were 391 patients referred for concern of an AEFI following either mRNA COVID-19 vaccine….
>
> Our study showed that nearly 90% of patients with first dose allergic symptoms tolerated the second dose with no recurrence of symptoms and all but one had symptoms that were mild and self-limited. The majority of reactions in our study were self-reported symptoms without objective findings of anaphylaxis."

Clin Transl Allergy: Protocol of safe vaccination against COVID-19 in patients with high risk of allergic reactions (17 May 2022)

> "Background: Sars-CoV-2 infections are hazardous, especially to the elderly and patients with comorbidities. With no efficient treatment available, newly developed vaccines are the only way to change the course of the pandemic. However, reports of allergic reactions

> resulted in some patients and practicing physicians being concerned about the safety of vaccine administration, particularly in people with severe anaphylactic reactions to multiple or unknown factors in their medical history.This study aimed to develop an allergic work-up protocol based on skin prick tests (SPT), intradermal testing (IDT) and intramuscular provocations, and desensitisation which may contribute to diagnosis and management of anti-COVID-19 vaccine allergy.
>
> Methods: Two hundred and eighty-five patients were enrolled. Two hundred and five of them entered the study based on severe anaphylactic reaction to unknown or multiple factors in their medical history which disqualified them for standard treatment. Another 80 patients were enrolled after developing an allergic reaction to the first dose of one such vaccine. In all subjects, SPT and IDT were performed. Serum tryptase was assessed in 79 patients randomly chosen from the study group.
>
> Results: Two hundred and seventy-seven patients with negative tests were given a vaccine without complications. Seven patients had positive skin tests. In two cases, tests confirmed Comirnaty allergy, while the other five confirmed solely skin sensitisation with no exposure prior to the study. Six patients with positive tests received titrated challenge using desensitisation protocol with a reasonable tolerance. One patient did not consent to desensitisation and one patient resigned despite negative tests. Overall, 283 (99%) patients were vaccinated using this newly developed protocol. Patients with adverse reactions to the first dose of the vaccine before the study had a significantly lower basal serum tryptase concentration ($p = 0.001$).
>
> Conclusion: Skin tests with anti-COVID-19 vaccines are a useful tool in the vaccination protocol. This protocol enables safe immunisation of high-allergy-risk patients even in cases of positive skin tests."

Breakthrough Infections, Reinfections, and Coinfections

Journal Articles

Lancet Oncol: Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): a population-based test-negative case-control study (23 May 2022)

> "Background: People with cancer are at increased risk of hospitalisation and death following infection with SARS-CoV-2. Therefore, we aimed to conduct one of the first evaluations of vaccine effectiveness against breakthrough SARS-CoV-2 infections in patients with cancer at a population level.

> Methods: In this population-based test-negative case-control study of the UK Coronavirus Cancer Evaluation Project (UKCCEP), we extracted data from the UKCCEP registry on all SARS-CoV-2 PCR test results (from the Second Generation Surveillance System), vaccination records (from the National Immunisation Management Service), patient demographics, and cancer records from England, UK, from Dec 8, 2020, to Oct 15, 2021. Adults (aged ≥18 years) with cancer in the UKCCEP registry were identified via Public Health England's Rapid Cancer Registration Dataset between Jan 1, 2018, and April 30, 2021, and comprised the cancer cohort. We constructed a control population cohort from adults with PCR tests in the UKCCEP registry who were not contained within the Rapid Cancer Registration Dataset. The coprimary endpoints were overall vaccine effectiveness against breakthrough infections after the second dose (positive PCR COVID-19 test) and vaccine effectiveness against breakthrough infections at 3–6 months after the second dose in the cancer cohort and control population.
>
> Findings: The cancer cohort comprised 377 194 individuals, of whom 42 882 had breakthrough SARS-CoV-2 infections. The control population consisted of 28 010 955 individuals, of whom 5 748 708 had SARS-CoV-2 breakthrough infections. Overall vaccine effectiveness was 69·8% (95% CI 69·8–69·9) in the control population and 65·5% (65·1–65·9) in the cancer cohort. Vaccine effectiveness at 3–6 months was lower in the cancer cohort (47·0%, 46·3–47·6) than in the control population (61·4%, 61·4–61·5).
>
> Interpretation: COVID-19 vaccination is effective for individuals with cancer, conferring varying levels of protection against breakthrough infections. However, vaccine effectiveness is lower in patients with cancer than in the general population. COVID-19 vaccination for patients with cancer should be used in conjunction with non-pharmacological strategies and community-based antiviral treatment programmes to reduce the risk that COVID-19 poses to patients with cancer."

Clin Infect Dis: Reduced Odds of SARS-CoV-2 Reinfection after Vaccination among New York City Adults, July-November 2021 (20 May 2022)

> "Background: Belief that vaccination is not needed for individuals with prior infection contributes to COVID-19 vaccine hesitancy. Among individuals infected with SARS-CoV-2 before vaccines became available, we assessed whether vaccinated individuals had reduced odds of reinfection.
>
> Methods: We conducted a case-control study among adult New York City residents who tested positive for SARS-CoV-2 infection in 2020, did not test positive again >90 days after initial positive test through July 1, 2021, and did not die before July 1, 2021. Case-patients with reinfection during July-November 2021 and control subjects with no reinfection were matched (1:3) on age, sex, timing of initial positive test in 2020, and neighborhood poverty

> level. Matched odds ratios (mOR) and 95% confidence intervals (CI) were calculated using conditional logistic regression.
>
> Results: Of 349,827 eligible adults, 2,583 were reinfected during July-November 2021. Of 2,401 with complete matching criteria data, 1,102 (45.9%) were known to be symptomatic for COVID-19-like-illness, and 96 (4.0%) were hospitalized. Unvaccinated individuals, compared with individuals fully vaccinated within the prior 90 days, had elevated odds of reinfection (mOR, 3.21; 95% CI, 2.70, 3.82), of symptomatic reinfection (mOR, 2.97; 95% CI, 2.31, 3.83), and of reinfection with hospitalization (mOR, 2.09; 95% CI, 0.91, 4.79). All three vaccines authorized or approved for use in the U.S. were similarly effective.
>
> Conclusion: Vaccination reduced odds of reinfections when the Delta variant predominated. Further studies should assess risk of severe outcomes among reinfected persons as new variants emerge, infection- and vaccine-induced immunity wanes, and booster doses are administered."

Treatments and Management

News in Brief

"As reports of ‘Paxlovid rebound’ increase, Covid researchers scramble for answers" (STAT; see also: CDC HAN noted below).

"FDA rejects antidepressant seen as possible Covid-19 treatment" (STAT).

"Can AI predict whether COVID patients will live or die? This tool shows doctors who is more at risk" (Euronews; see also: CODOP tool).

Special Reports and Other Resources

CDC: HAN Health Advisory: COVID-19 Rebound After Paxlovid Treatment [pdf] (24 May 2022)

> "The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to update healthcare providers, public health departments, and the public on the potential for recurrence of COVID-19 or “COVID-19 rebound.” Paxlovid continues to be recommended for earlystage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease. Paxlovid treatment helps prevent hospitalization and death due to COVID-19. COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. A brief return

> of symptoms may be part of the natural history of SARS-CoV-2 (the virus that causes COVID-19) infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status. Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Paxlovid or other anti-SARS-CoV-2 therapies in cases where COVID-19 rebound is suspected."

Journal Articles

Eur Rev Med Pharmacol Sci: Persistence of procoagulable thromboelastography results in hospitalized COVID-19 patients despite clinical improvement (20 May 2022)

> "Objective: COVID-19 patients have been shown to be hypercoagulable, increasing the risk for thromboembolic events. The kinetics of the blood coagulation process were monitored daily throughout hospitalization in COVID-19 positive patients.
>
> Patients and methods: Thromboelastography (TEG) was used to assess blood coagulation in 48 adult patients hospitalized for COVID-19 in this prospective cohort study. Clinical risk was assessed via National Early Warning Scores (NEWS) for each day of hospitalization.
>
> Results: During hospitalization, 98% of patients had one or more procoagulable TEG result. Thromboelastography results remained prothrombotic upon discharge in 80% of patients. NEWS significantly decreased by discharge compared to the peak scores.
>
> Conclusions: Overall, patients were discharged from the hospital with significant clinical improvement, but without abnormal TEG results returning to a normal range. All patients in our study survived and few had thromboembolic events, so if and for how long these patients remain at risk for future complications warrants further investigation."

Clin Infect Dis: Transfusing convalescent plasma as post-exposure prophylaxis against SARS-CoV-2 infection: a double-blinded, phase 2 randomized, controlled trial (17 May 2022)

> "Background: The efficacy of SARS-CoV-2 convalescent plasma (CCP) for preventing infection in exposed, uninfected individuals is unknown. CCP might prevent infection when administered before symptoms or laboratory evidence of infection.
>
> Methods: This double-blinded, phase 2 randomized, controlled trial (RCT) compared the efficacy and safety of prophylactic high titer (≥1:320 by Euroimmun ELISA) CCP with standard plasma. Asymptomatic participants aged ≥18 years with close contact exposure to a person with confirmed COVID-19 in the previous 120 hours and negative SARS-CoV-2 test within 24 hours before transfusion were eligible. The primary outcome was new SARS-CoV-2 infection.

> Results: 180 participants were enrolled; 87 were assigned to CCP and 93 to control plasma, and 170 transfused at 19 sites across the United States from June 2020 to March 2021. Two were excluded for screening SARS-CoV-2 RT-PCR positivity. Of the remaining 168 participants, 12/81 (14·8%) CCP and 13/87 (14·9%) control recipients developed SARS-CoV-2 infection; 6 (7·4%) CCP and 7 (8%) control recipients developed COVID-19 (infection with symptoms). There were no COVID-19-related hospitalizations in CCP and 2 in control recipients. Efficacy by restricted mean infection free time (RMIFT) by 28 days for all SARS-CoV-2 infections (25·3 vs. 25·2 days; p = 0·49) and COVID-19 (26·3 vs. 25·9 days; p = 0·35) was similar for both groups.
>
> Conclusions: Administration of high-titer CCP as post-exposure prophylaxis, while appearing safe, did not prevent SARS-CoV-2 infection."

CMAJ: The risk of death or unplanned readmission after discharge from a COVID-19 hospitalization in Alberta and Ontario (16 May 2022)

> "Background: The frequency of readmissions after COVID-19 hospitalizations is uncertain, as is whether current readmission prediction equations are useful for discharge risk stratification of COVID-19 survivors or for comparing among hospitals. We sought to determine the frequency and predictors of death or unplanned readmission after a COVID-19 hospital discharge.
>
> Methods: We conducted a retrospective cohort study of all adults (≥ 18 yr) who were discharged alive from hospital after a nonpsychiatric, nonobstetric, acute care admission for COVID-19 between Jan. 1, 2020, and Sept. 30, 2021, in Alberta and Ontario.
>
> Results: Of 843 737 individuals who tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction during the study period, 46 412 (5.5%) were adults admitted to hospital within 14 days of their positive test. Of these, 8496 died in hospital and 34 846 were discharged alive (30 336 discharged after an index admission of ≤ 30 d and 4510 discharged after an admission > 30 d). One in 9 discharged patients died or were readmitted within 30 days after discharge (3173 [10.5%] of those with stay ≤ 30 d and 579 [12.8%] of those with stay > 30 d). The LACE score (length of stay, acuity, Charlson Comorbidity Index and number of emergency visits in previous 6 months) for predicting urgent readmission or death within 30 days had a c-statistic of 0.60 in Alberta and 0.61 in Ontario; inclusion of sex, discharge locale, deprivation index and teaching hospital status in the model improved the c-statistic to 0.73.
>
> Interpretation: Death or readmission after discharge from a COVID-19 hospitalization is common and had a similar frequency in Alberta and Ontario. Risk stratification and interinstitutional comparisons of outcomes after hospital admission for COVID-19 should include sex, discharge locale and socioeconomic measures, in addition to the LACE variables."

JAMA: Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial (15 May 2022)

> "Question: Does prone positioning reduce endotracheal intubation in adults who were awake and not intubated and who had hypoxemic respiratory failure from COVID-19?
>
> Findings: In this randomized clinical trial that included 400 adults with acute hypoxemic respiratory failure from COVID-19, awake prone positioning compared with usual care resulted in endotracheal intubation at 30 days in 34.1% vs 40.5% of participants, respectively. Although the hazard ratio was 0.81, the result was not statistically significant.
>
> Meaning: Although the findings do not support prone positioning in this setting, the effect size for the primary study outcome was imprecise and does not exclude a clinically important benefit."

Long COVID and Other Post-Infectious Findings

News in Brief

"4 questions about long Covid experts wish they could answer" (Vox).

"'That's just part of aging': long covid symptoms are often overlooked in seniors" (KHN).

Special Reports and Other Resources

FAIR Health: Patients Diagnosed with Post-COVID Conditions [pdf] (18 May 2022)

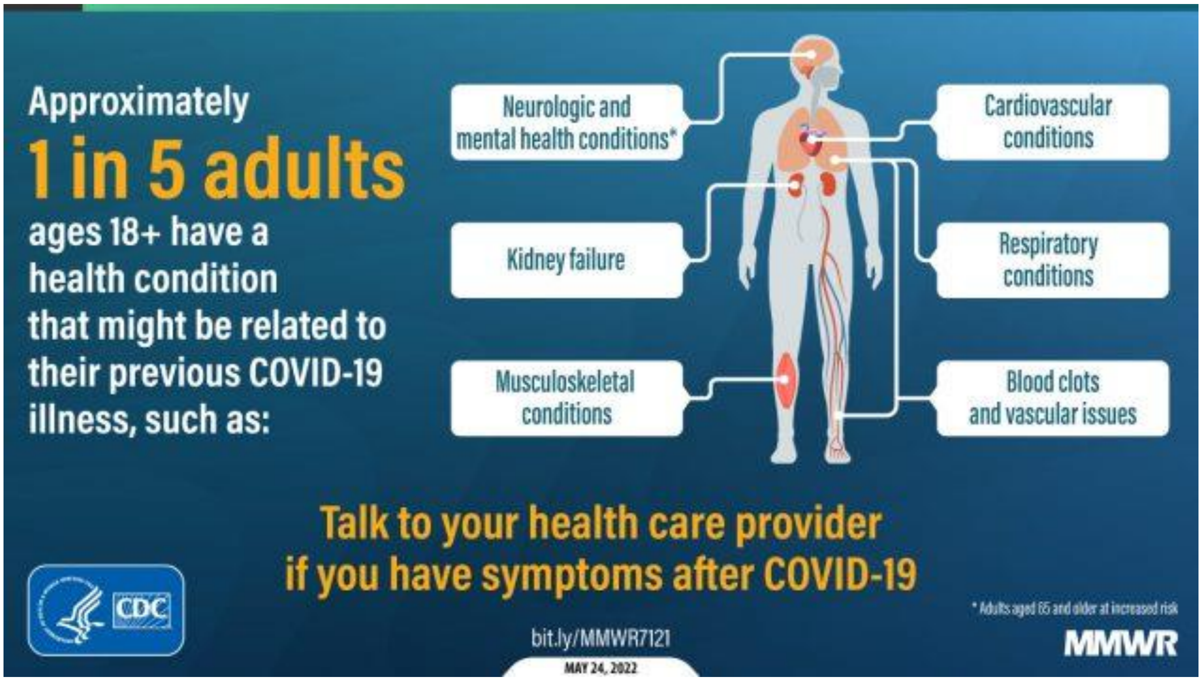
> "Post-COVID conditions, also known by such terms as long COVID and post-acute sequelae of COVID-19, have become an issue of growing national concern. Until recently, researchers were limited by the lack of a specific ICD-10 diagnosis code for post-COVID conditions. Effective October 1, 2021, ICD-10 code U09.9 was introduced for "post COVID-19 condition, unspecified."
>
> This report is among the first to use the U09.9 code for research purposes. Drawing on longitudinal data from FAIR Health's repository of billions of private healthcare claims, this report studies the population of 78,252 patients in the repository who were diagnosed with the U09.9 code from October 1, 2021, to January 31, 2022. That population is analyzed by COVID-19 hospitalizations, age, gender, number of days from initial COVID-19 diagnosis to last post-COVID diagnosis during the study period, preexisting chronic comorbidities, co-occurring diagnoses and risk scores.

Among the key findings:

- The majority (75.8 percent) of patients diagnosed with a U09.9 post-COVID condition had not been hospitalized for COVID-19.
- Among patients who presented with a U09.9 post-COVID diagnosis, 81.6 percent of females had not had a COVID-19 hospitalization compared to 67.5 percent of males.
- The age group 36 to 50 was the most likely to be diagnosed with U09.9 post-COVID conditions; 34.6 percent of patients with that diagnosis were in that age group.
- Females were more likely than males to be diagnosed with U09.9 post-COVID conditions. Females made up 59.8 percent of the population of patients with that diagnosis, while males made up 40.2 percent. By comparison, within the cohort of people diagnosed with COVID-19 in the FAIR Health repository, 53.8 percent of patients were female and 46.2 percent were male.
- Of patients who presented with a U09.9 post-COVID condition, 30.7 percent had no identified preexisting chronic comorbidities.
- The three diagnoses most commonly co-occurring on the same claim line with the U09.9 postCOVID diagnosis in patients across all ages and genders were abnormalities of breathing (23.2 percent of patients with post-COVID conditions), cough (18.9 percent) and malaise and fatigue (16.7 percent).
- In patients with a U09.9 post-COVID diagnosis, certain co-occurring diagnoses were more common in some age groups than across all age groups: for example, multisystem inflammatory syndrome in patients aged 0 to 12; abnormalities of heartbeat in the age group 13 to 22; generalized anxiety disorder in patients aged 23 to 35; and hypertensive diseases in the age group 65 and older.
- "Other and unspecified myopathies" (diseases that affect the muscles that control voluntary movement) occurred in patients in the post-COVID population 11.1 times more often than in the same population prior to COVID-19. Pulmonary embolism occurred 2.6 times more often. "Other disorders of brain," including post-viral fatigue syndrome and certain forms of encephalopathy, occurred two times more often.
- On average, in all age groups, patients with a U09.9 post-COVID condition had higher Department of Health & Human Services-Hierarchical Condition Category (HHS-HCC) risk scores after their diagnosis of COVID-19 than before. HHS-HCC risk scores identify which patients are likely to consume more healthcare resources and potentially incur more healthcare-related costs in the long run."

Journal Articles

MMWR: Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021 (24 May 2022)


Approximately
1 in 5 adults
ages 18+ have a health condition that might be related to their previous COVID-19 illness, such as:
Neurologic and mental health conditions*
Cardiovascular conditions
Kidney failure
Respiratory conditions
Musculoskeletal conditions
Blood clots and vascular issues
Talk to your health care provider if you have symptoms after COVID-19
* Adults aged 65 and older at increased risk
CDC
bit.ly/MMWR7121
MAY 24, 2022
MMWR

"What is already known about this topic? As more persons are exposed to and infected by SARS-CoV-2, reports of patients who experience persistent symptoms or organ dysfunction after acute COVID-19 and develop post-COVID conditions have increased.

What is added by this report? COVID-19 survivors have twice the risk for developing pulmonary embolism or respiratory conditions; one in five COVID-19 survivors aged 18–64 years and one in four survivors aged ≥65 years experienced at least one incident condition that might be attributable to previous COVID-19.

What are the implications for public health practice? Implementation of COVID-19 prevention strategies, as well as routine assessment for post-COVID conditions among persons who survive COVID-19, is critical to reducing the incidence and impact of post-COVID conditions, particularly among adults aged ≥65 years."

Radiology: Lung Abnormalities Depicted with Hyperpolarized Xenon MRI in Patients with Long COVID (24 May 2022)

"Background: Post-Covid-19 condition describes symptoms following COVID-19 infection after four weeks. Symptoms are wide-ranging but breathlessness is common.

> Purpose: The purpose of this study was to determine whether the previously described lung abnormalities on Hp-XeMRI in post-hospitalised COVID-19 participants are also present in non-hospitalised participants with Post-Covid-19 condition.
>
> Methods: In this prospective study, non-hospitalised Post-Covid-19 condition (NHLC) and post-hospitalised COVID-19 (PHC) participants were enrolled from 06/2020 to 08/2021. Participants had chest CT, hyperpolarized pulmonary 129Xenon MRI (Hp-XeMRI), pulmonary function tests, 1-minute sit-to-stand test and breathlessness questionnaires. Control subjects underwent HP-XeMRI only. CT scans were analysed for post COVID interstitial lung disease severity using a previously published scoring system, and Full-scale Airway Network (FAN) modelling. Analysis used group and pair-wise comparisons between participants and controls, and correlations between participant clinical and imaging data.
>
> Results: A total of 11 NHLC (4:7 Male: Female, 44 ± 11 years, [37-50], (mean ± SD, [95% CI]) and 12 PHC (10:2, Male: Female, 58 ± 10 years, [52-64]) participants were included, with a significant difference in age between groups, p = 0.05. NHLC participants were 287 ± 79, [240-334] and PHC 143 ± 72, [105-190] days from infection, respectively. NHLC and PHC participants had normal or near normal CT scans (0.3/25 ± 0.6, [0-0.63] and 7/25 ± 5, [4-10], respectively). Gas transfer (DLco (%)) was different between NHLC and PHC participants (76 ± 8%, [73-83] vs 86 ± 8%, [80-91] respectively, p = 0.04) but there was no evidence of other differences in lung function. Red Blood Cell:Tissue Plasma (RBC:TP) mean was different between volunteers vs PHC (0.45 ± 0.07, [0.43-0.47] vs (0.31 ± 0.10, [0.24-0.37], respectively, p = 0.02) and volunteers vs NHLC (0.37 ± 0.10, [0.31-0.44], p = 0.03) participants, but not between NHLC and PHC participants (p = 0.26). FAN results did not correlate with DLco or Hp- XeMRI.
>
> Conclusion: NHLC and PHC subjects showed Hp-XeMRI RBC:TP abnormalities, with NHLC participants demonstrating lower DLco than PHC participants despite having normal CT scans."

See also: editorial

Ann Clin Transl Neurol: Evolution of neurologic symptoms in non-hospitalized COVID-19 "long haulers" (24 May 2022)

"Objective: We characterized the evolution of neurologic symptoms and self-perceived recovery of non-hospitalized COVID-19 "long haulers" 6-9 months after their initial Neuro-COVID-19 clinic evaluation.

> Methods: In this follow-up study on the first 100 patients, 50 SARS-CoV-2 laboratory-positive (SARS-CoV-2+), and 50 laboratory-negative (SARS-CoV-2-), evaluated at our Neuro-COVID-19 clinic between May and November 2020, patients completed phone

> questionnaires on their neurologic symptoms, subjective impression of recovery and quality of life.
>
> Results: Of 52 patients who completed the study (27 SARS-CoV-2+ , 25 SARS-CoV-2-) a median 14.8 (range 11-18) months after symptom onset, mean age was 42.8 years, 73% were female, and 77% were vaccinated for SARS-CoV-2. Overall, there was no significant change in the frequency of most neurologic symptoms between first and follow-up evaluations, including "brain fog" (81 vs. 71%), numbness/tingling (69 vs. 65%), headache (67 vs. 54%), dizziness (50 vs. 54%), blurred vision (34 vs. 44%), tinnitus (33 vs. 42%), and fatigue (87 vs. 81%). However, dysgeusia and anosmia decreased overall (63 vs. 27%, 58 vs. 21%, both $p < 0.001$). Conversely, heart rate and blood pressure variation (35 vs. 56%, $p = 0.01$) and gastrointestinal symptoms (27 vs. 48%, $p = 0.04$) increased at follow-up. Patients reported improvements in their recovery, cognitive function, and fatigue, but quality of life measures remained lower than the US normative population ($p < 0.001$). SARS-CoV-2 vaccination did not have a positive or detrimental impact on cognitive function or fatigue.
>
> Interpretation: Non-hospitalized COVID-19 "long haulers" continue to experience neurologic symptoms, fatigue, and compromised quality of life 14.8 months after initial infection."

JAMA Netw Open: Viral Antigen and Inflammatory Biomarkers in Cerebrospinal Fluid in Patients With COVID-19 Infection and Neurologic Symptoms Compared With Control Participants Without Infection or Neurologic Symptoms (23 May 2022)

> "Question: Are cerebrospinal fluid (CSF) SARS-CoV-2 antigens associated with central nervous system inflammation in patients with COVID-19?
>
> Findings: Of 44 patients with COVID-19 (23 neurosymptomatic) included in this hospital-based cross-sectional study, CSF nucleocapsid antigen was detectable in 89% of patients with available data and was significantly correlated with immune activation markers (neopterin and interferon γ). Moreover, neurosymptomatic patients had a more pronounced inflammatory CSF profile compared with neuroasymptomatic patients that could not be attributed to differences in COVID-19 severity.
>
> Meaning: These results suggest that viral components may contribute to central nervous system immune responses without direct viral invasion and highlight the clinical importance of neurologic symptoms."

Nat Med: A multisystem, cardio-renal investigation of post-COVID-19 illness (23 May 2022)

> "The pathophysiology and trajectory of post-Coronavirus Disease 2019 (COVID-19) syndrome is uncertain. To clarify multisystem involvement, we undertook a prospective cohort study including patients who had been hospitalized with COVID-19 (ClinicalTrials.gov ID NCT04403607). Serial blood biomarkers, digital electrocardiography and patient-reported outcome measures were obtained in-hospital and at 28-60 days post-discharge when

> multisystem imaging using chest computed tomography with pulmonary and coronary angiography and cardio-renal magnetic resonance imaging was also obtained. Longer-term clinical outcomes were assessed using electronic health records. Compared to controls (n = 29), at 28-60 days post-discharge, people with COVID-19 (n = 159; mean age, 55 years; 43% female) had persisting evidence of cardio-renal involvement and hemostasis pathway activation. The adjudicated likelihood of myocarditis was 'very likely' in 21 (13%) patients, 'probable' in 65 (41%) patients, 'unlikely' in 56 (35%) patients and 'not present' in 17 (11%) patients. At 28-60 days post-discharge, COVID-19 was associated with worse health-related quality of life (EQ-5D-5L score 0.77 (0.23) versus 0.87 (0.20)), anxiety and depression (PHQ-4 total score 3.59 (3.71) versus 1.28 (2.67)) and aerobic exercise capacity reflected by predicted maximal oxygen utilization (20.0 (7.6) versus 29.5 (8.0) ml/kg/min) (all P < 0.01). During follow-up (mean, 450 days), 24 (15%) patients and two (7%) controls died or were rehospitalized, and 108 (68%) patients and seven (26%) controls received outpatient secondary care (P = 0.017). The illness trajectory of patients after hospitalization with COVID-19 includes persisting multisystem abnormalities and health impairments that could lead to substantial demand on healthcare services in the future."

J Appl Physiol: The effect of medium-term recovery status after COVID-19 illness on cardiopulmonary exercise capacity in a physically active adult population (19 May 2022)

> "Background: A failure to fully recover following coronavirus disease 2019 (COVID-19) may have a profound impact on high functioning populations ranging from front-line emergency services to professional or amateur/recreational athletes.
>
> Aim: To describe the medium-term cardiopulmonary exercise profiles of individuals with 'persistent symptoms' and individuals who feel 'recovered' after hospitalization or mild-moderate community infection following COVID-19 to an age, sex and job-role matched control group.
>
> Methods: 113 participants underwent cardiopulmonary functional tests at a mean 159±7 days (~5 months) following acute illness; 27 hospitalized with persistent symptoms (hospitalized-symptomatic), 8 hospitalized and now recovered (hospitalized-recovered); 34 community managed with persistent symptoms (community-symptomatic); 18 community managed and now recovered (community-recovered), and 26 controls.
>
> Results: Hospitalized groups had the least favorable body composition (body mass, body mass index and waist circumference) compared to controls. Hospitalized-symptomatic and community-symptomatic individuals had a lower oxygen uptake (V̇O2) at peak exercise (hospitalized-symptomatic, 29.9±5.0ml/kg/min; community-symptomatic, 34.4±7.2ml/kg/min; vs. control 43.9±3.1ml/kg/min, both p<0.001). Hospitalized-symptomatic individuals had a steeper V̇E/V̇CO2 slope (lower ventilatory efficiency) (30.5±5.3 vs. 25.5±2.6, p=0.003) vs. controls. Hospitalized-recovered had a significantly

> lower oxygen uptake at peak (32.6±6.6ml/kg/min vs. 43.9 ±13.1ml/kg/min, p=0.015) compared to controls. No significant differences were reported between community-recovered individuals and controls in any cardiopulmonary parameter.
>
> Conclusion: Medium term findings suggest community-recovered individuals did not differ in cardiopulmonary fitness from physically active healthy controls. This suggests their readiness to return to higher levels of physical activity. However, the hospitalized-recovered group and both groups with persistent symptoms had enduring functional limitations, warranting further monitoring, rehabilitation and recovery."

BMJ: Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study (18 May 2022)

> "Objective: To estimate associations between covid-19 vaccination and long covid symptoms in adults with SARS-CoV-2 infection before vaccination.
>
> Design: Observational cohort study.
>
> Setting: Community dwelling population, UK.
>
> Participants: 28 356 participants in the Office for National Statistics COVID-19 Infection Survey aged 18-69 years who received at least one dose of an adenovirus vector or mRNA covid-19 vaccine after testing positive for SARS-CoV-2 infection.
>
> Main outcome measure: Presence of long covid symptoms at least 12 weeks after infection over the follow-up period 3 February to 5 September 2021.
>
> Results: Mean age of participants was 46 years, 55.6% (n=15 760) were women, and 88.7% (n=25 141) were of white ethnicity. Median follow-up was 141 days from first vaccination (among all participants) and 67 days from second vaccination (83.8% of participants). 6729 participants (23.7%) reported long covid symptoms of any severity at least once during follow-up. A first vaccine dose was associated with an initial 12.8% decrease (95% confidence interval -18.6% to -6.6%, P<0.001) in the odds of long covid, with subsequent data compatible with both increases and decreases in the trajectory (0.3% per week, 95% confidence interval -0.6% to 1.2% per week, P=0.51). A second dose was associated with an initial 8.8% decrease (95% confidence interval -14.1% to -3.1%, P=0.003) in the odds of long covid, with a subsequent decrease by 0.8% per week (-1.2% to -0.4% per week, P<0.001). Heterogeneity was not found in associations between vaccination and long covid by sociodemographic characteristics, health status, hospital admission with acute covid-19, vaccine type (adenovirus vector or mRNA), or duration from SARS-CoV-2 infection to vaccination.
>
> Conclusions: The likelihood of long covid symptoms was observed to decrease after covid-19 vaccination and evidence suggested sustained improvement after a second dose, at least

> over the median follow-up of 67 days. Vaccination may contribute to a reduction in the population health burden of long covid, although longer follow-up is needed."
>
> See also: editorial

Lancet Digit Health: Identifying who has long COVID in the USA: a machine learning approach using N3C data (16 May 2022)

> "Background: Post-acute sequelae of SARS-CoV-2 infection, known as long COVID, have severely affected recovery from the COVID-19 pandemic for patients and society alike. Long COVID is characterised by evolving, heterogeneous symptoms, making it challenging to derive an unambiguous definition. Studies of electronic health records are a crucial element of the US National Institutes of Health's RECOVER Initiative, which is addressing the urgent need to understand long COVID, identify treatments, and accurately identify who has it—the latter is the aim of this study.
>
> Methods: Using the National COVID Cohort Collaborative's (N3C) electronic health record repository, we developed XGBoost machine learning models to identify potential patients with long COVID. We defined our base population (n=1 793 604) as any non-deceased adult patient (age ≥18 years) with either an International Classification of Diseases-10-Clinical Modification COVID-19 diagnosis code (U07.1) from an inpatient or emergency visit, or a positive SARS-CoV-2 PCR or antigen test, and for whom at least 90 days have passed since COVID-19 index date. We examined demographics, health-care utilisation, diagnoses, and medications for 97 995 adults with COVID-19. We used data on these features and 597 patients from a long COVID clinic to train three machine learning models to identify potential long COVID among all patients with COVID-19, patients hospitalised with COVID-19, and patients who had COVID-19 but were not hospitalised. Feature importance was determined via Shapley values. We further validated the models on data from a fourth site.
>
> Findings: Our models identified, with high accuracy, patients who potentially have long COVID, achieving areas under the receiver operator characteristic curve of 0·92 (all patients), 0·90 (hospitalised), and 0·85 (non-hospitalised). Important features, as defined by Shapley values, include rate of health-care utilisation, patient age, dyspnoea, and other diagnosis and medication information available within the electronic health record.
>
> Interpretation: Patients identified by our models as potentially having long COVID can be interpreted as patients warranting care at a specialty clinic for long COVID, which is an essential proxy for long COVID diagnosis as its definition continues to evolve. We also achieve the urgent goal of identifying potential long COVID in patients for clinical trials. As more data sources are identified, our models can be retrained and tuned based on the needs of individual studies."

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Physiol Int: The associations of long-COVID symptoms, clinical characteristics and affective psychological constructs in a non-hospitalized cohort (16 May 2022)

> "Objective: The effects of COVID-19, especially long-COVID, on the psychological health is incompletely understood. We aimed to evaluate the mid-term associations of the long-COVID symptoms and affective factors in a cohort of non-hospitalized patients.
>
> Method: A total of 166 patients were enrolled in this study, including 119 sedentary/non-athlete and 47 athlete subjects at the Post-COVID Outpatient Clinic of Semmelweis University. Clinical data regarding acute and long-term symptoms were obtained and detailed laboratory testing was carried out. Demographic data and psychological tests were collected.
>
> Results: We found a positive association between the level of depressive symptoms and anxiety and long-COVID symptom count, while life satisfaction and social support correlated negatively with the long-COVID symptom count. Higher haemoglobin levels and lower LDL-cholesterol were also shown to be moderating factors. A regression model showed that symptoms during acute infection, depression, age, and life satisfaction are predictors of the long-COVID symptom count. The presence of pre-existing affective or anxiety problems was also associated with higher reported long-COVID symptom count. Furthermore, we found significant association between pre-existing mental health problems and the investigated psychological constructs.
>
> Conclusion: It appears that long COVID-19 is associated with acute symptoms and mental factors. Depression and anxiety have been shown to have a negative effect on symptom perception, and also contribute to a higher number of symptoms in a non-hospitalized sample. Our study suggests bi-directional interconnection between clinical and psychological factors."

Pregnancy, Postpartum Period, and Women's Health

Journal Articles

Clin Infect Dis: Maternal and Neonatal SARS-CoV-2 Omicron Variant Neutralization after Antenatal mRNA Vaccination (24 May 2022)

> "We evaluated the neutralization efficiency against SARS-CoV-2 omicron variant in maternal and cord blood sera after antenatal BNT162b2 vaccination. Neutralizing antibodies against omicron were lacking at the time of delivery after two-dose vaccination. A third booster dose was essential in building neutralizing antibody capacity against omicron among mothers and neonates."

Fam Pract: Mortality in COVID-19 among women on hormone replacement therapy: a retrospective cohort study (17 May 2022)

> "Background: Limited recent observational data have suggested that there may be a protective effect of oestrogen on the severity of COVID-19 disease. Our aim was to investigate the association between hormone replacement therapy (HRT) or combined oral contraceptive pill (COCP) use and the likelihood of death in women with COVID-19.
>
> Methods: We undertook a retrospective cohort study using routinely collected computerized medical records from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database. We identified a cohort of 1,863,478 women over 18 years of age from 465 general practices in England. Mixed-effects logistic regression models were used to quantify the association between HRT or COCP use and all-cause mortality among women diagnosed with confirmed or suspected COVID-19 in unadjusted and adjusted models.
>
> Results: There were 5,451 COVID-19 cases within the cohort. HRT was associated with a reduction in all-cause mortality in COVID-19 (adjusted OR 0.22, 95% CI 0.05 to 0.94). There were no reported events for all-cause mortality in women prescribed COCPs. This prevented further examination of the impact of COCP.
>
> Conclusions: We found that HRT prescription within 6 months of a recorded diagnosis of COVID-19 infection was associated with a reduction in all-cause mortality. Further work is needed in larger cohorts to examine the association of COCP in COVID-19, and to further investigate the hypothesis that oestrogens may contribute a protective effect against COVID-19 severity."

Pediatric Population

News in Brief

Vaccines and Boosters

"Pfizer/BioNTech to seek Covid vaccine authorization for children under age 5" (STAT).

"FDA expands eligibility for Pfizer-BioNTech COVID-19 vaccine booster dose to children 5 through 11 years" (FDA).

"CDC recommends Covid boosters for kids ages 5 to 11 after advisory committee vote" (STAT).

"The FDA will meet mid-June to discuss pediatric COVID vaccine authorization requests from Pfizer/BioNTech (for kids 6 months to 4 years) and from Moderna (for kids 6 months to 17 years)" (Medpage).

"Pfizer-BioNTech COVID-19 vaccine demonstrates strong immune response, high efficacy and favorable safety in children 6 months to under 5 years of age following third dose" (Pfizer).

Hepatitis

As of this writing, 216 cases are under investigation for hepatitis of unknown etiology in children (CDC).

Technical report: "Guidance for diagnostic testing of cases with severe acute hepatitis of unknown aetiology in children" (ECDC).

"Puzzling pediatric hepatitis cases echo an earlier mysterious illness" (STAT).

Journal Articles

NEJM: Evaluation of mRNA-1273 Covid-19 Vaccine in Children 6 to 11 Years of Age (26 May 2022)

> "Background: Vaccination of children to prevent coronavirus disease 2019 (Covid-19) is an urgent public health need. The safety, immunogenicity, and efficacy of the mRNA-1273 vaccine in children 6 to 11 years of age are unknown.
>
> Methods: Part 1 of this ongoing phase 2-3 trial was open label for dose selection; part 2 was an observer-blinded, placebo-controlled expansion evaluation of the selected dose. In part 2, we randomly assigned children (6 to 11 years of age) in a 3:1 ratio to receive two injections of mRNA-1273 (50 µg each) or placebo, administered 28 days apart. The primary objectives were evaluation of the safety of the vaccine in children and the noninferiority of the immune response in these children to that in young adults (18 to 25 years of age) in a related phase 3 trial. Secondary objectives included determination of the incidences of confirmed Covid-19 and severe acute respiratory syndrome coronavirus 2 infection, regardless of symptoms. Interim analysis results are reported.
>
> Results: In part 1 of the trial, 751 children received 50-µg or 100-µg injections of the mRNA-1273 vaccine, and on the basis of safety and immunogenicity results, the 50-µg dose level was selected for part 2. In part 2 of the trial, 4016 children were randomly assigned to receive two injections of mRNA-1273 (50 µg each) or placebo and were followed for a median of 82 days (interquartile range, 14 to 94) after the first injection. This dose level was associated with mainly low-grade, transient adverse events, most commonly injection-site pain, headache, and fatigue. No vaccine-related serious adverse events, multisystem

> inflammatory syndrome in children, myocarditis, or pericarditis were reported as of the data-cutoff date. One month after the second injection (day 57), the neutralizing antibody titer in children who received mRNA-1273 at a 50-µg level was 1610 (95% confidence interval [CI], 1457 to 1780), as compared with 1300 (95% CI, 1171 to 1443) at the 100-µg level in young adults, with serologic responses in at least 99.0% of the participants in both age groups, findings that met the prespecified noninferiority success criterion. Estimated vaccine efficacy was 88.0% (95% CI, 70.0 to 95.8) against Covid-19 occurring 14 days or more after the first injection, at a time when B.1.617.2 (delta) was the dominant circulating variant.
>
> Conclusions: Two 50-µg doses of the mRNA-1273 vaccine were found to be safe and effective in inducing immune responses and preventing Covid-19 in children 6 to 11 years of age; these responses were noninferior to those in young adults."

Clin Infect Dis: Comparison of influenza and COVID-19-associated hospitalizations among children < 18 years old in the United States-FluSurv-NET (October-April 2017-2021) and COVID-NET (October 2020-September 2021) (20 May 2022)

> "Background: Influenza virus and SARS-CoV-2 are significant causes of respiratory illness in children.
>
> Methods: Influenza and COVID-19-associated hospitalizations among children <18 years old were analyzed from FluSurv-NET and COVID-NET, two population-based surveillance systems with similar catchment areas and methodology. The annual COVID-19-associated hospitalization rate per 100 000 during the ongoing COVID-19 pandemic (October 1, 2020-September 30, 2021) was compared to influenza-associated hospitalization rates during the 2017-18 through 2019-20 influenza seasons. In-hospital outcomes, including intensive care unit (ICU) admission and death, were compared.
>
> Results: Among children <18 years old, the COVID-19-associated hospitalization rate (48.2) was higher than influenza-associated hospitalization rates: 2017-18 (33.5), 2018-19 (33.8), and 2019-20 (41.7). The COVID-19-associated hospitalization rate was higher among adolescents 12-17 years old (COVID-19: 59.9; influenza range: 12.2-14.1), but similar or lower among children 5-11 (COVID-19: 25.0; influenza range: 24.3-31.7) and 0-4 (COVID-19: 66.8; influenza range: 70.9-91.5) years old. Among children <18 years old, a higher proportion with COVID-19 required ICU admission compared with influenza (26.4% vs 21.6%; p < 0.01). Pediatric deaths were uncommon during both COVID-19- and influenza-associated hospitalizations (0.7% vs 0.5%; p = 0.28).
>
> Conclusions: In the setting of extensive mitigation measures during the COVID-19 pandemic, the annual COVID-19-associated hospitalization rate during 2020-2021 was higher among adolescents and similar or lower among children <12 years old compared with influenza during the three seasons before the COVID-19 pandemic. COVID-19 adds substantially to

> the existing burden of pediatric hospitalizations and severe outcomes caused by influenza and other respiratory viruses."

JAMA: Severity and Incidence of Multisystem Inflammatory Syndrome in Children During 3 SARS-CoV-2 Pandemic Waves in Israel (19 May 2022)

> "This study suggests that MIS-C during the Omicron wave was less severe than during the Alpha or Delta waves of the COVID-19 pandemic. Possible explanations include the Omicron variant itself, previous infection with SARS-CoV-2, vaccination against SARS-CoV-2, and improvement in treatment over time. In addition, the incidence rate of MIS-C during the Omicron wave was lower than during the Delta and Alpha waves."

JAMA Netw Open: Association of Congenital and Acquired Cardiovascular Conditions With COVID-19 Severity Among Pediatric Patients in the US (17 May 2022)

> "Question: What is the association between individual congenital and acquired cardiovascular conditions and COVID-19 severity in pediatric patients?
>
> Findings: In this cohort study of 171 416 US individuals aged 2 months to 17 years with SARS-CoV-2 infection, cardiac arrest, cardiogenic shock, heart surgery, cardiopulmonary disease, heart failure, hypotension, nontraumatic cerebral hemorrhage, pericarditis, and biventricular defects were associated with increased COVID-19 severity.
>
> Meaning: The findings suggest that previous or preexisting cardiovascular conditions are associated with increased COVID-19 severity, in varying degrees, in pediatric patients."

JAMA: Association of Prior BNT162b2 COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection in Children and Adolescents During Omicron Predominance (13 May 2022)

> "Question: Does the estimated effectiveness of 2 doses of the BNT162b2 COVID-19 vaccine against symptomatic SARS-CoV-2 Omicron variant infection (based on the odds ratio for the association of prior vaccination and infection) wane rapidly among children and adolescents, as has been observed for adults?
>
> Findings: In a test-negative, case-control study conducted from December 2021 to February 2022 during Omicron variant predominance that included 121 952 tests from sites across the US, estimated vaccine effectiveness against symptomatic infection for children 5 to 11 years of age was 60.1% 2 to 4 weeks after dose 2 and 28.9% during month 2 after dose 2. Among adolescents 12 to 15 years of age, estimated vaccine effectiveness was 59.5% 2 to 4 weeks after dose 2 and 16.6% during month 2; estimated booster dose effectiveness in adolescents 2 to 6.5 weeks after the booster was 71.1%.
>
> Meaning: Among children and adolescents, estimated vaccine effectiveness for 2 doses of BNT162b2 against symptomatic infection decreased rapidly, and among adolescents increased after a booster dose."

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JAMA: Risk of Infection and Hospitalization Among Vaccinated and Unvaccinated Children and Adolescents in New York After the Emergence of the Omicron Variant (13 May 2022)

> "The risks of infection and hospitalization were elevated for unvaccinated vs vaccinated children aged 5 to 11 and 12 to 17 years, although the risk declined as Omicron became more prevalent. Protection declined with time since vaccination. These results complement recent findings of reduced vaccine effectiveness for adolescents against the Delta variant and the dual effects of the variant and waning protection against infection, with sustained protection against hospitalizations."

Healthcare Workers

Journal Articles

PLoS Med: Antibody responses against SARS-CoV-2 variants induced by four different SARS-CoV-2 vaccines in health care workers in the Netherlands: A prospective cohort study (17 May 2022)

> "Background: Emerging and future SARS-CoV-2 variants may jeopardize the effectiveness of vaccination campaigns. Therefore, it is important to know how the different vaccines perform against diverse SARS-CoV-2 variants.
>
> Methods and findings: In a prospective cohort of 165 SARS-CoV-2 naive health care workers in the Netherlands, vaccinated with either one of four vaccines (BNT162b2, mRNA-1273, AZD1222 or Ad26.COV2.S), we performed a head-to-head comparison of the ability of sera to recognize and neutralize SARS-CoV-2 variants of concern (VOCs; Alpha, Beta, Gamma, Delta and Omicron). Repeated serum sampling was performed 5 times during a year (from January 2021 till January 2022), including before and after booster vaccination with BNT162b2. Four weeks after completing the initial vaccination series, SARS-CoV-2 wild-type neutralizing antibody titers were highest in recipients of mRNA-1273, followed by recipients of BNT162b2 (geometric mean titers (GMT) of 358 [95% CI 231-556] and 214 [95% CI 153-299], respectively; $p<0.05$), and substantially lower in those vaccinated with the adenovirus vector-based vaccines AZD1222 and Ad26.COV2.S (GMT of 18 [95% CI 11-30] and 14 [95% CI 8-25] IU/ml, respectively; $p<0.001$). VOCs neutralization was reduced in all vaccine groups, with the greatest reduction in neutralization GMT observed against the Omicron variant (fold change 0.03 [95% CI 0.02-0.04], $p<0.001$). The booster BNT162b2 vaccination increased neutralizing antibody titers for all groups with substantial improvement against the VOCs including the Omicron variant. We used linear regression and linear mixed model analysis. All results were adjusted for possible confounding of age and sex. Study limitations include the lack of cellular immunity data.

> Conclusions: Overall, this study shows that the mRNA vaccines appear superior to adenovirus vector-based vaccines in inducing neutralizing antibodies against VOCs four weeks after initial vaccination and after booster vaccination, which implies the use of mRNA vaccines for both initial and booster vaccination."

PLoS One: A national study of moral distress among U.S. internal medicine physicians during the COVID-19 pandemic (16 May 2022)

> "Background: There have been no studies to date of moral distress during the COVID-19 pandemic in national samples of U.S. health workers. The purpose of this study was to determine, in a national sample of internal medicine physicians (internists) in the U.S.: 1) the intensity of moral distress; 2) the predictors of moral distress; 3) the outcomes of moral distress.
>
> Methods: We conducted a national survey with an online panel of internists, representative of the membership of the American College of Physicians, the largest specialty organization of physicians in the United States, between September 21 and October 8, 2020. Moral distress was measured with the Moral Distress Thermometer, a one-item scale with a range of 0 ("none") to 10 ("worst possible"). Outcomes were measured with short screening scales.
>
> Results: The response rate was 37.8% (N = 810). Moral distress intensity was low (mean score = 2.4, 95% CI, 2.2-2.6); however, 13.3% (95% CI, 12.1% - 14.5%) had a moral distress score greater than or equal to 6 ("distressing"). In multiple linear regression models, perceived risk of death if infected with COVID-19 was the strongest predictor of higher moral distress (β (standardized regression coefficient) = 0.26, p < .001), and higher perceived organizational support (respondent belief that their health organization valued them) was most strongly associated with lower moral distress (β = -0.22, p < .001). Controlling for other factors, high levels of moral distress, but not low levels, were strongly associated (adjusted odds ratios 3.0 to 11.5) with screening positive for anxiety, depression, posttraumatic stress disorder, burnout, and intention to leave patient care.
>
> Conclusions: The intensity of moral distress among U.S. internists was low overall. However, the 13% with high levels of moral distress had very high odds of adverse mental health outcomes. Organizational support may lower moral distress and thereby prevent adverse mental health outcomes."

Sci Rep: A machine learning approach to predict resilience and sickness absence in the healthcare workforce during the COVID-19 pandemic (16 May 2022)

> "During the COVID-19 pandemic, healthcare workers (HCWs) have faced unprecedented workloads and personal health risks leading to mental disorders and surges in sickness absence. Previous work has shown that interindividual differences in psychological

> resilience might explain why only some individuals are vulnerable to these consequences. However, no prognostic tools to predict individual HCW resilience during the pandemic have been developed. We deployed machine learning (ML) to predict psychological resilience during the pandemic. The models were trained in HCWs of the largest Finnish hospital, Helsinki University Hospital (HUS, N = 487), with a six-month follow-up, and prognostic generalizability was evaluated in two independent HCW validation samples (Social and Health Services in Kymenlaakso: Kymsote, N = 77 and the City of Helsinki, N = 322) with similar follow-ups never used for training the models. Using the most predictive items to predict future psychological resilience resulted in a balanced accuracy (BAC) of 72.7-74.3% in the HUS sample. Similar performances (BAC = 67-77%) were observed in the two independent validation samples. The models' predictions translated to a high probability of sickness absence during the pandemic. Our results provide the first evidence that ML techniques could be harnessed for the early detection of COVID-19-related distress among HCWs, thereby providing an avenue for potential targeted interventions."

Front Glob Womens Health: Secondary Traumatic Stress and Moral Injury in Maternity Care Providers: A Narrative and Exploratory Review (04 May 2022)

> "Introduction: A significant percentage of maternity providers have experienced secondary traumatic stress following a traumatic birth. Previous studies identified it as an issue, but this literature review is 5-9 years old. In addition, the construct of moral injury has significantly increased our understanding of secondary trauma for military veterans. In the wake of COVID-19, this construct also applies to healthcare providers.
>
> Objectives: The present article updates these reviews and compares findings for three groups: labor and delivery nurses, midwives, and obstetricians. The second portion of this review re-examines previously published qualitative research to determine whether moral injury might more accurately describe the experiences of maternity personnel.
>
> Methods: A comprehensive review of PubMed, Scopus, Web of Science, PsychINFO, and CINAHL was conducted in June 2021 using search terms such as compassion fatigue, secondary trauma, moral injury, labor and delivery, nurses, midwives, and obstetricians. Forty articles were identified, but only 16 focused on secondary trauma or moral injury.
>
> Results: Secondary trauma is a significant concern affecting at least 25% of maternity staff. However, some countries have very low rates, which correspond to low rates in childbirth-related trauma in mothers. Secondary trauma can lead to several symptoms, including re-experiencing, avoidance, negative changes in mood and cognitions, and hyperarousal, which can cause significant impairment. As a result, many providers decide to leave the field in the wake of a traumatic birth. The incidence of moral injury is unknown, but a re-examination of previously published qualitative data suggests that this construct, generally used to describe combat veterans, does describe some of what providers have reported.

> Acts of omission, i.e., failure to stop the harmful acts of others had long-term negative effects on labor and delivery nurses, consistent with data from military samples. Two possible mediators were proposed: hierarchical and gendered relationships in hospitals and agency of care.
>
> Conclusion: The effects of traumatic birth on providers can be severe, including possible psychological sequelae, impaired job performance, and leaving the field. Moral injury expands upon the construct of secondary traumatic stress. This construct better describes the experiences of maternity staff in non-primary roles who witness traumatic births and are often haunted by events that they could not prevent, but often question whether they should have."

Mental Health and Wellness

Journal Articles

Scand J Work Environ Health: Effects of workplace measures against COVID-19 on psychological distress of full-time employees: A 12-month prospective study in the COVID-19 pandemic (16 May 2022)

> "Objective: This study aimed to investigate the prospective effects of corporate and organizational workplace measures against COVID-19 on reducing employees` psychological distress during a 12-month follow-up in the COVID-19 pandemic.
>
> Methods: Data were retrieved from an online longitudinal panel survey of full-time employees in Japan, with the 1st survey in March 2020, and the 2nd to 6th surveys in May, August, November 2020, February and March 2021, respectively. Seven area-specific workplace measures were assessed using a self-report 23-item scale at the 2nd follow-up. Psychological distress was measured using an 18-item scale of the Brief Job Stress Questionnaire at each survey. Linear regressions and mixed model analysis were conducted of psychological distress at follow-ups on scores of the area-specific workplace measures, adjusting for psychological distress and other covariates at the 1st survey.
>
> Results: A total of 941 employees responded at baseline; most of them (86.9-90.9%) participated in the follow-up surveys. Linear regression analysis indicated that workplace measures of facilitating employees' preventive measures (ie, hygiene behaviors) statistically significantly and negatively correlated with psychological distress at the 5th survey [b=-0.518, standard error (SE) 0.259, P=0.046]. A statistically significant and negative interaction between the scores and time of follow-up was observed in the mixed model analysis (b=-

> 0.096, SE 0.047, P=0.041). No such correlation or interaction was found for any of other subcategorical workplace measures.
>
> Conclusions: The study provides prospective evidence for a protective effect of workplace measures to facilitate employee's hygiene behaviors on reducing psychological distress of full-time employees in the COVID-19 pandemic. The association seems stronger at a later follow-up."

Other Infectious Diseases and Public Health Threats

News in Brief

"Home testing for syphilis gains support in wake of COVID: With cases of sexually transmitted infections growing, researchers hope self-tests — made popular by the pandemic — could stem the tide" (Nature).

"Viruses that were on hiatus during Covid are back — and behaving in unexpected ways" (STAT).

"There are now 10 confirmed cases of Legionnaires' disease in the Bronx, according to city health officials who also say the investigation into the cluster continues" (NBC NY).

Wild poliovirus in Mozambique (Reuters), avian influenza in commercial and backyard flocks across the US (USDA), and *Salmonella* in chocolate (FDA)… maybe it's just me, but it's challenging to not conclude that something has it in for humanity.

Smallpox

"How Rahima came to hold a special place in smallpox history — and help ensure its end" (NPR).

Meanwhile, the FDA has approved the intravenous formulation of TPOXX (tecovirimat) for the treatment of smallpox (SIGA).

Relatedly, see the special topic section below on monkeypox.

Long Reads

This article was originally published 2 years ago, but it feels timely: "How climate change is contributing to skyrocketing rates of infectious disease" (ProPublica).

Journal Articles

Infect Control Hosp Epidemiol: Trends in facility-level rates of Clostridioides difficile infections in US hospitals, 2019-2020 (19 May 2022)

> "Objectives: The coronavirus disease 2019 pandemic caused substantial changes to healthcare delivery and antibiotic prescribing beginning in March 2020. To assess pandemic impact on Clostridioides difficile infection (CDI) rates, we described patients and trends in facility-level incidence, testing rates, and percent positivity during 2019-2020 in a large cohort of US hospitals.
>
> Methods: We estimated and compared rates of community-onset CDI (CO-CDI) per 10,000 discharges, hospital-onset CDI (HO-CDI) per 10,000 patient days, and C. difficile testing rates per 10,000 discharges in 2019 and 2020. We calculated percent positivity as the number of inpatients diagnosed with CDI over the total number of discharges with a test for C. difficile. We used an interrupted time series (ITS) design with negative binomial and logistic regression models to describe level and trend changes in rates and percent positivity before and after March 2020.
>
> Results: In pairwise comparisons, overall CO-CDI rates decreased from 20.0 to 15.8 between 2019 and 2020 ($P < .0001$). HO-CDI rates did not change. Using ITS, we detected decreasing monthly trends in CO-CDI (-1% per month, $P = .0036$) and HO-CDI incidence (-1% per month, $P < .0001$) during the baseline period, prior to the COVID-19 pandemic declaration. We detected no change in monthly trends for CO-CDI or HO-CDI incidence or percent positivity after March 2020 compared with the baseline period.
>
> Conclusions: While there was a slight downward trajectory in CDI trends prior to March 2020, no significant change in CDI trends occurred during the COVID-19 pandemic despite changes in infection control practices, antibiotic use, and healthcare delivery."

Ann intern Med: Human Papillomavirus Vaccine Impact and Effectiveness Through 12 Years After Vaccine Introduction in the United States, 2003 to 2018 (17 May 2022)

> "Background: Human papillomavirus (HPV) vaccination was introduced in 2006 for females and in 2011 for males.
>
> Objective: To estimate vaccine impact and effectiveness against quadrivalent HPV vaccine (4vHPV)-type prevalent infection among sexually experienced U.S. females and vaccine effectiveness for sexually experienced U.S. males.
>
> Design: NHANES (National Health and Nutrition Examination Survey) conducted in 2003 to 2006 (prevaccine era) and in 2007 to 2010, 2011 to 2014, and 2015 to 2018 (vaccine eras).
>
> Setting: Nationally representative U.S. surveys.

> Participants: Sexually experienced participants aged 14 to 24 years.
>
> Intervention: U.S. HPV vaccination program.
>
> Measurements: Participant-collected cervicovaginal and penile specimens were tested for HPV DNA. The prevalences of 4vHPV and non-4vHPV types were estimated in each era for females and in 2013 to 2016 for males. Prevalences among the female population overall, vaccinated females, and unvaccinated females were compared in vaccine eras versus the prevaccine era (vaccine impact). Within each vaccine era, prevalence among vaccinated females was compared with that among unvaccinated females (vaccine effectiveness). Vaccine impact and effectiveness were estimated as (1 - prevalence ratio) · 100.
>
> Results: Among sexually experienced females aged 14 to 24 years, the impact on 4vHPV-type prevalence in 2015 to 2018 was 85% overall, 90% among vaccinated females, and 74% among unvaccinated females. No significant declines were found in non-4vHPV-type prevalence. Vaccine effectiveness ranged from 60% to 84% during vaccine eras for females and was 51% during 2013 to 2016 for males.
>
> Limitation: Self- or parent-reported vaccination history and small numbers in certain subgroups limited precision.
>
> Conclusion: Nationally representative data show increasing impact of the vaccination program and herd protection. Vaccine effectiveness estimates will be increasingly affected by herd effects."

Emerg Infect Dis: Effects of Acute Dengue Infection on Sperm and Virus Clearance in Body Fluids of Men (02 May 2022)

> "We investigated the effects of dengue virus (DENV) on semen using samples collected 7, 15, 30, 60, and 90 days after symptom onset from 10 infected volunteers on Réunion Island. We assessed characteristics of semen and reproductive hormones and isolated motile spermatozoa from semen. We assayed semen for DENV using reverse transcription PCR and searched for DENV RNA by virus isolation in Vero E6 cell cultures. Four volunteers had >1 DENV RNA-positive semen samples; 2 volunteers had DENV RNA–positive semen at day 15 and 1 at day 30. No motile sperm were DENV positive. After exposure to positive semen, few Vero E6 cells stained positive for DENV antigens, indicating low levels of replicative virus. We found DENV had shorter duration in semen than in blood. These findings support the possibilities that DENV is sexually transmissible for a short period after acute dengue illness and that acute dengue induces reversible alterations in sperm."

Special Topic: Monkeypox

News in Brief

"Multi-country monkeypox outbreak in non-endemic countries" (WHO).

Want to get a big picture view of suspected and confirmed cases of monkeypox? Check out the Monkeypox Tracker.

Global Spread

"African scientists baffled by monkeypox cases in Europe, US" (AP).

"Monkeypox goes global: why scientists are on alert: Scientists are trying to understand why the virus, a less lethal relative of smallpox, has cropped up in so many populations around the world" (Nature).

"EU health agency warns monkeypox could become endemic in Europe if outbreak continues" (STAT).

"The mystery of monkeypox's global spread: Initial genomic sequencing suggests the virus hasn't mutated to become more transmissible. So what explains its unprecedented rise across the world?" (Wired)

In the US

"A CDC expert answers questions on monkeypox" (STAT).

"Biden says quarantines for monkeypox aren't needed in U.S." (WP).

Vaccines

"WHO says no urgent need for mass monkeypox vaccinations" (Reuters); "WHO says monkeypox 'containable' as more govts start limited vaccinations" (Reuters).

The US government is buying millions of doses of a vaccine that prevents both smallpox and monkeypox (Newsweek).

"Gov't seeks monkeypox vaccine from stockpile amid possible U.S. cases" (UPI).

Webinars and Events

CDC COCA: What Clinicians Need to Know about Monkeypox in the United States and Multiple Countries (recorded 24 May 2022)

CDC Media Telebriefing: Update on 2022 U.S. Monkeypox Investigation (23 May 2022)

Special Reports and Other Resources

JHCHS: Monkeypox Fact Sheet [pdf] (updated 20 May 2022)

CDC: HAN Health Advisory: Monkeypox Virus Infection in the United States and Other Non-endemic Countries—2022 [pdf] (20 May 2022)

> "The Massachusetts Department of Public Health and the Centers for Disease Control and Prevention (CDC) are investigating a confirmed case of monkeypox in the United States. On May 17, 2022, skin lesions that had several features suspicious for monkeypox—firm, well circumscribed, deep-seated, and umbilicated lesions—on a Massachusetts resident prompted specialized Laboratory Response Network (LRN) testing of swab specimens collected from the resident; preliminary testing confirmed the presence of DNA consistent with an orthopoxvirus using Orthopoxvirus generic and non-variola Orthopoxvirus realtime polymerase chain reaction (PCR) assays. This group of viruses includes monkeypox virus (the causative agent of monkeypox). Testing at CDC on May 18 confirmed the patient was infected with a West African strain of monkeypox virus. The patient is currently isolated and does not pose a risk to the public.
>
> Cases of monkeypox have previously been identified in travelers from, or residents of, West African or Central African countries where monkeypox is considered to be endemic. CDC is issuing this Health Alert Network (HAN) Health Advisory to ask clinicians in the United States to be vigilant to the characteristic rash associated with monkeypox. Suspicion for monkeypox should be heightened if the rash occurs in people who 1) traveled to countries with recently confirmed cases of monkeypox, 2) report having had contact with a person or people who have a similar appearing rash or received a diagnosis of confirmed or suspected monkeypox, or 3) is a man who regularly has close or intimate in-person contact with other men, including those met through an online website, digital application ("app"), or at a bar or party. Lesions may be disseminated or located on the genital or perianal area alone. Some patients may present with proctitis, and their illness could be clinically confused with a sexually transmitted infection (STI) like syphilis or herpes, or with varicella zoster virus infection."

Journal Articles

A collection of selected readings on monkeypox:
https://www.ncbi.nlm.nih.gov/sites/myncbi/tracy.shields.1/collections/61880953/public/

Lancet Infect Dis: Clinical features and management of human monkeypox: a retrospective observational study in the UK (24 May 2022)

"Background: Cases of human monkeypox are rarely seen outside of west and central Africa. There are few data regarding viral kinetics or the duration of viral shedding and no licensed treatments. Two oral drugs, brincidofovir and tecovirimat, have been approved for treatment of smallpox and have demonstrated efficacy against monkeypox in animals. Our aim was to describe the longitudinal clinical course of monkeypox in a high-income setting, coupled with viral dynamics, and any adverse events related to novel antiviral therapies.

Methods: In this retrospective observational study, we report the clinical features, longitudinal virological findings, and response to off-label antivirals in seven patients with monkeypox who were diagnosed in the UK between 2018 and 2021, identified through retrospective case-note review. This study included all patients who were managed in dedicated high consequence infectious diseases (HCID) centres in Liverpool, London, and Newcastle, coordinated via a national HCID network.

Findings: We reviewed all cases since the inception of the HCID (airborne) network between Aug 15, 2018, and Sept 10, 2021, identifying seven patients. Of the seven patients, four were men and three were women. Three acquired monkeypox in the UK: one patient was a health-care worker who acquired the virus nosocomially, and one patient who acquired the virus abroad transmitted it to an adult and child within their household cluster. Notable disease features included viraemia, prolonged monkeypox virus DNA detection in upper respiratory tract swabs, reactive low mood, and one patient had a monkeypox virus PCR-positive deep tissue abscess. Five patients spent more than 3 weeks (range 22–39 days) in isolation due to prolonged PCR positivity. Three patients were treated with brincidofovir (200 mg once a week orally), all of whom developed elevated liver enzymes resulting in cessation of therapy. One patient was treated with tecovirimat (200mg twice daily for 2 weeks orally), experienced no adverse effects, and had a shorter duration of viral shedding and illness (10 days hospitalisation) compared with the other six patients. One patient experienced a mild relapse 6 weeks after hospital discharge.

Interpretation: Human monkeypox poses unique challenges, even to well resourced health-care systems with HCID networks. Prolonged upper respiratory tract viral DNA shedding after skin lesion resolution challenged current infection prevention and control guidance. There is an urgent need for prospective studies of antivirals for this disease."

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